

Distributional Behavior of Diffusion Coefficients Obtained by Single Trajectories in Annealed Transit Time Model

Takuma Akimoto & Eiji Yamamoto

Graduate School of Science and Technology, Keio University, Yokohama, 223-8522, Japan

E-mail: akimoto@keio.jp

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Abstract. Local diffusion coefficients in disordered systems such as spin glass systems and living cells are highly heterogeneous and may change over time. Such a time-dependent and spatially heterogeneous environment results in irreproducibility of single-particle-tracking measurements. Irreproducibility of time-averaged observables has been theoretically studied in the context of weak ergodicity breaking in stochastic processes. Here, we provide rigorous descriptions of equilibrium and non-equilibrium diffusion processes for the annealed transit time model, which is a heterogeneous diffusion model in living cells. We give analytical solutions for the mean square displacement (MSD) and the relative standard deviation of the time-averaged MSD for equilibrium and non-equilibrium situations. We find that the time-averaged MSD grows linearly with time and that the diffusion coefficients are intrinsically random in non-equilibrium situations. Our findings pave the way for a theoretical understanding of distributional behavior of the diffusion coefficients in disordered systems.

Keywords: anomalous diffusion, ergodicity, non-equilibrium processes

1. Introduction

Transporting biological molecules in living cells plays a key role in biochemical interactions, transmembrane signaling, and efficient reactions. In single-particle tracking (SPT), the motion of proteins or lipids is tracked to determine directly the diffusivity and to understand the biological role of diffusivity. Therefore, it is expected that SPT experiments will provide new insight into molecular transport in living cells. In fact, many SPT experiments reveal anomalous dynamics such as subdiffusion, aging, fluctuating diffusivity, and heterogeneous environments in living cells [1, 2, 3, 4, 5, 6].

Mean square displacement (MSD) is the most popular observable for characterizing the diffusivity of particles. There are two different averaging procedures for calculating

the MSD. One is the ensemble average, and the other is the time average. The time-averaged MSD is defined as

$$\overline{\delta^2(\Delta; t)} \equiv \frac{1}{t - \Delta} \int_0^{t-\Delta} dt' [\mathbf{r}(t' + \Delta) - \mathbf{r}(t')]^2, \quad (1)$$

where $\mathbf{r}(t')$ is the position of a particle at time t' tracked by the SPT experiments and t is the total measurement time. In stationary stochastic processes, these two averages are equivalent with the aid of the law of large numbers. This equivalence is one of the properties of ergodicity. While ergodicity is a concept in dynamical systems, an observable in a stochastic system is called ergodic if the time averages of the observable for different realizations converge uniquely to the ensemble average in equilibrium. This property ensures the reproducibility of measurements in experiments [7]: long SPT measurements give the same result under the same experimental setup. However, it was reported in SPT experiments in living cells that this reproducibility breaks down [2, 3, 4, 6, 8, 9], where the time-averaged MSD for a fixed Δ does not converge to a constant but fluctuates randomly across in realizations (random diffusion coefficient). Further, other experiments also reveal that time averages of observables such as occupation time and intensity of fluorescence fail to converge to a constant in some non-equilibrium systems [10, 11, 12]. While there are several distributional limit theorems related to distributional behaviors of time averages in probability theory [13, 14, 15], little is known about the relationship between the stochastic models used in probability theory and the systems in experiments. Therefore, a theoretical foundation of irreproducibility is an important and challenging problem in statistical physics.

Ergodicity gives a mathematical guarantee that time averages are equal to the ensemble average, i.e., it ensures reproducibility [16]. Mathematically, infinite ergodic theory generalizes the concept of ergodicity, and states that time-averaged observables remain random even in the long-time limit [17, 18]. Thus, it is expected that infinite ergodic theory will play a fundamental role in understanding random transport coefficients observed in SPT trajectories [19, 20, 21]. However, ergodicity in stochastic processes has been studied in a different way. If there is a highly stuck region in phase space, a particle cannot explore the whole phase space due to the trapping in the stuck region. Such a situation is called weak ergodicity breaking [22]. When a system shows weak ergodicity breaking, a time-averaged observable does not converge to a constant even when the measurement time goes to infinity [23, 24, 25]. However, distributional behavior of time-averaged observables can be observed in homogeneous systems. In simple random walk, the time-averaged occupation time that a random walker resides in positive region does not converge to a constant but converges in distribution, known as the generalized arcsine law [26]. Thus, some time-averaged observables in homogeneous environments do not converge to constants but converge in distribution. Such a time-averaged observable is not reproducible but has a distributional reproducibility because the distribution is universal in the sense that it does not depend on initial ensembles. In stochastic models of anomalous diffusion, several distributional limit theorems for random diffusion coefficients have been studied

to elucidate irreproducibility [23, 24, 27, 28, 25, 29]. However, there are experimental results which cannot be explained by such stochastic models [6]. The goal of this paper is to fill the gap between experimentally observed irreproducibility and distributional limit theorems in theoretical models.

To consider the irreproducibility of the time-averaged MSD in diffusion in living cells, we investigate the annealed transit time model (ATTM) [30], which has been shown to describe heterogeneous diffusion in living cells [6]. The authors of [30] show anomalous diffusion and aging of the time-averaged MSD. However, the distributional behavior of the time-averaged MSD remains an open problem. Moreover, the exact descriptions of the governing equations for the propagator have not been found so far. In this paper, we describe the equations rigorously and solve them analytically. Within this model, we show that the time-averaged MSD remains random even in the long measurement times, i.e., the diffusion coefficients are irreproducible but have distributional reproducibility in the sense that the distribution of the time time-averaged MSD is universal.

2. Model

In living cells, diffusivity strongly depends on space as well as time, that is, it is heterogeneous diffusion. One of the simplest models describing such a heterogeneous diffusion process is the Langevin equation with fluctuating diffusivity [31, 32],

$$\frac{d\mathbf{r}(t)}{dt} = \sqrt{2D(t)}\mathbf{w}(t), \quad (2)$$

where $\mathbf{r}(t)$ is the n -dimensional position of a particle at time t and $D(t)$ is a stochastic process. Such a fluctuating diffusivity results from a fluctuating medium driven by fluctuations of friction or temperature [33, 34, 35], diffusion in two-layer medium [36, 37], or fluctuations of a diffusing particle's shape. In [38, 32], dichotomous processes are used for $D(t)$ to investigate effects of the underlying stochastic process $D(t)$ on physical features of the time-averaged MSD. To consider heterogeneous diffusion in living cells, we have to model the stochastic process of $D(t)$. In a previous study, the ATTM was proposed for modeling heterogeneous diffusion in living cells, where the diffusion coefficient is constant for a random sojourn time and the constant depends on the sojourn time [30]. When we consider quenched environment with heterogeneous local diffusivities, sojourn times in slow and high diffusive regions will imply long and short times, respectively. Thus, it is physically natural to assume that the sojourn time is inversely coupled to the diffusion coefficient. Moreover, it is important to consider the annealed model like Eq. (2) because the annealed framework enables us to treat analytical calculations, heterogeneous environments in cells may not provide quenched environments, and the annealed model is considered to be a good approximation for the quenched model. In this paper, we assume that the diffusion coefficient is coupled to the sojourn time, i.e., $D_\tau = \tau^{\sigma-1}$ ($0 < \sigma < 1$) as in [30]. In non-equilibrium situations, the probability density function (PDF) $\rho(\tau)$ of the sojourn time follows a power-law with

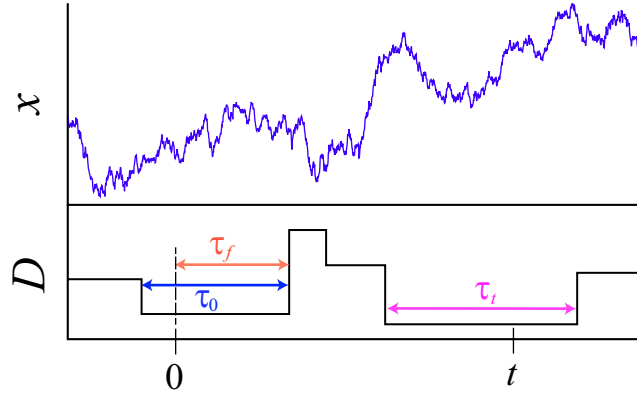


Figure 1. Time series $x(t)$ and the underlying diffusion process $D(t)$ ($\sigma = 0.1$). The first sojourn time (τ_0), the forward recurrence time (τ_f), and the sojourn time at time t (τ_t) are shown in the lower panel.

no finite mean:

$$\rho(\tau) \sim \frac{c}{|\Gamma(-\alpha)|} \tau^{-1-\alpha} \quad (\tau \rightarrow \infty), \quad (3)$$

where c is a scale parameter. A power-law sojourn-time distribution is observed in super-cooled liquids [39] and can be derived with $\alpha = 0.5$ in the first passage time. The mean sojourn time diverges for $\alpha \leq 1$, which means that there is no finite characteristic time in the process. In other words, this process is an intrinsic non-equilibrium process.

3. Recurrence time distributions

Here we provide several recurrence time distributions studied in renewal theory [40, 41]. As shown in Fig. 2, the underlying diffusion process at time $t = 0$, $D(0)$, is determined by the first sojourn time τ_0 and not by the forward recurrence time τ_f . Therefore, one must consider recurrence time distributions to describe the exact equations for the propagator in the equilibrium situation. By the same technique in [41], the Laplace transform of the joint PDF $f(\tau_t, \tau_f; t)$ of the sojourn time at time t , $\tau_t \equiv \tau_{N_t}$, and the forward recurrence time at time t , $\tau_f \equiv t_{N_t+1} - t$, is given by

$$\begin{aligned} \hat{f}(k, u; s) &\equiv \int_0^\infty \int_0^\infty \int_0^\infty d\tau_t d\tau_f dt e^{-k\tau_t} e^{-u\tau_f} e^{-st} f(\tau_t, \tau_f; t) \\ &= \sum_{n=0}^\infty \left\langle e^{-k\tau_{n+1} - ut_{n+1}} \int_{t_n}^{t_{n+1}} dt e^{-(s-u)t} \right\rangle = \frac{\hat{\rho}(k+s) - \hat{\rho}(k+u)}{u-s} \frac{1}{1 - \hat{\rho}(s)}, \quad (4) \end{aligned}$$

where N_t is the number of changes of states until time t , t_k is the time when the k th change of states occurs, and $\hat{\rho}(s)$ is the Laplace transform of $\rho(\tau)$. In equilibrium process, the system started at $t = -\infty$, and we start to observe from $t = 0$ [40]. Thus, we have the double Laplace transform of the joint PDF $f_{\text{eq}}(\tau_t, \tau_f)$ of τ_t and τ_f in equilibrium process:

$$\hat{f}_{\text{eq}}(k, u) = \lim_{s \rightarrow 0} s \hat{f}(k, u; s) = \frac{\hat{\rho}(k) - \hat{\rho}(k+u)}{\langle \tau \rangle u}, \quad (5)$$

where $\langle \tau \rangle \equiv \int_0^\infty \rho(\tau) d\tau$ is the mean sojourn time. The inverse Laplace transform with respect to k and u yields

$$f_{\text{eq}}(\tau_t, \tau_f) = \frac{\rho(\tau_t)\theta(\tau_t - \tau_f)}{\langle \tau \rangle}, \quad (6)$$

where $\theta(t) = 1$ if $t > 0$ and $\theta(t) = 0$ otherwise. Integrating Eq. (6) with respect to τ_f yields the PDF $\rho_{\text{eq}}(\tau)$ of the sojourn times at $t = 0$ in equilibrium (τ_t for $t \rightarrow \infty$):

$$\rho_{\text{eq}}(\tau) = \int_0^\infty f_{\text{eq}}(\tau, \tau_f) d\tau_f = \frac{\tau \rho(\tau)}{\langle \tau \rangle}. \quad (7)$$

The mean and the second moments of the initial diffusion coefficient $D(0)$ in equilibrium can be calculated as $\langle D(0) \rangle_{\text{eq}} \equiv \int_0^\infty d\tau D_\tau \rho_{\text{eq}}(\tau)$ and $\langle D(0)^2 \rangle_{\text{eq}} \equiv \int_0^\infty d\tau D_\tau^2 \rho_{\text{eq}}(\tau)$, and are assumed to be finite in equilibrium processes.

4. General framework

Let $P(\mathbf{r}, t)$ be the PDF of the position $\mathbf{r} = (r_1, \dots, r_n)$ at time t and $Q(\mathbf{r}, t)$ be the PDF of the position \mathbf{r} conditioned that the state of $D(t)$ changes at exactly time t . We assume that $P(\mathbf{r}, 0) = \delta(\mathbf{r})$. Hence, the PDFs satisfy the following generalized renewal equations:

$$Q(\mathbf{r}, t) = \int_{-\infty}^\infty dr'_1 \cdots \int_{-\infty}^\infty dr'_n \int_0^t dt' \psi(\mathbf{r}', t') Q(\mathbf{r} - \mathbf{r}', t - t') + \psi_0(\mathbf{r}, t), \quad (8)$$

$$P(\mathbf{r}, t; \tau) = \int_0^t dt' \Psi(\mathbf{r}', t'; \tau) Q(\mathbf{r} - \mathbf{r}', t - t') + \Psi_0(\mathbf{r}, t; \tau), \quad (9)$$

where $P(\mathbf{r}, t; \tau)$ is the PDF $P(\mathbf{r}, t)$ conditioned that the sojourn at t , τ_t , is given by τ , $\psi(\mathbf{r}, t)$ is the joint PDF of the displacement \mathbf{r} and the sojourn time t , $\psi_0(\mathbf{r}, t)$ is the joint PDF of the displacement \mathbf{r} and the first sojourn time t , $\Psi(\mathbf{r}, t; \tau)$ is the joint PDF of the displacement \mathbf{r} , the time elapsed t from t_{N_t} , and the last sojourn time (the sojourn time at t) τ . Finally, the PDF $P(\mathbf{r}, t)$ is

$$P(\mathbf{r}, t) = \int_0^\infty d\tau P(\mathbf{r}, t; \tau), \quad (10)$$

where $\Psi_0(\mathbf{r}, t; \tau)$ is the joint PDF of the displacement \mathbf{r} and the time elapsed t , and the sojourn time τ , and there is no renewal during t .

In ATTM, the joint PDF $\psi(\mathbf{r}, t)$ is given by $\psi(\mathbf{r}, t) = \phi(\mathbf{r}, t)\rho(t)$, where $\phi(\mathbf{r}, t)$ is a Gaussian propagator with diffusion coefficient $D_t = t^{\sigma-1}$:

$$\phi(\mathbf{r}, t) = \frac{1}{2\sqrt{n\pi D_t t}} \exp\left(\frac{-\mathbf{r}^2}{4nD_t t}\right). \quad (11)$$

Moreover, the joint PDF $\Psi(\mathbf{r}, t; \tau)$ is given by $\Psi(\mathbf{r}, t; \tau) = \rho(\tau)\phi(\mathbf{r}, t; \tau)\theta(\tau - t)$, where $\phi(\mathbf{r}, t; \tau)$ is a Gaussian propagator with diffusion coefficient $D_\tau = \tau^{\sigma-1}$:

$$\phi(\mathbf{r}, t; \tau) = \frac{1}{2\sqrt{n\pi D_\tau t}} \exp\left(\frac{-\mathbf{r}^2}{4nD_\tau t}\right), \quad (12)$$

and the joint PDF $\Psi_0(\mathbf{r}, t; \tau)$ is given by $\Psi_0(\mathbf{r}, t; \tau) = \phi(\mathbf{r}, t; \tau) \int_t^\infty f_{\text{eq}}(\tau, \tau_f) d\tau_f$. By the Fourier-Laplace transform, we have from Eqs. (8) and (9)

$$\hat{P}(\mathbf{k}, s) = \frac{1 + \hat{\psi}_0(\mathbf{k}, s)}{1 - \hat{\psi}(\mathbf{k}, s)} \int_0^\infty d\tau \hat{\Psi}(\mathbf{k}, s; \tau) + \int_0^\infty d\tau \hat{\Psi}_0(\mathbf{k}, s; \tau). \quad (13)$$

This is the exact representation of the Fourier-Laplace transform of the propagator, which is a generalization of the random walk framework [42, 43, 44, 45, 46].

Next, we derive moments of the time-averaged MSD. For $\Delta \ll t$, we approximate the time-averaged MSD as

$$\overline{\delta^2(\Delta; t)} \sim \frac{2n}{t} \left(\sum_{i=0}^{N_t} D_{\tau_i}(\tau_i) \tau_i + (t - t_{N_t}) D_{\tau_{N_t+1}}(\tau_{N_t+1}) \right) \Delta, \quad (14)$$

where N_t is the number of changes of states until time t , τ_i is the i th sojourn time, $t_i \equiv \tau_1 + \dots + \tau_i$, and $D_\tau(\tau)$ is the time-averaged diffusion coefficient under the diffusion coefficient D_τ : $D_\tau(\tau) \equiv \int_0^\tau \{\mathbf{r}(t' + \Delta) - \mathbf{r}(t')\}^2 dt' / (\tau \Delta)$. We further assume that $D_\tau(\tau) = D_\tau$:

$$\frac{t \overline{\delta^2(\Delta; t)}}{2n\Delta} \sim Z(t) \equiv \sum_{i=0}^{N_t} D_{\tau_i} \tau_i + D_{\tau_{N_t+1}} (t - t_{N_t}). \quad (15)$$

This assumption is considered to be valid in the asymptotic limit for t [32]. Let $P_D(z, t)$ be the PDF of $Z(t)$ and $Q_D(x, t)$ be the PDF of $Z(t)$ where a renewal occurs at exactly time t . We can write the generalized renewal equation for $Z(t)$:

$$Q_D(z, t) = \int_0^z dz' \int_0^t dt' \psi_D(z', t') Q_D(z - z', t - t') + \psi_D^0(z, t), \quad (16)$$

$$P_D(z, t; \tau) = \int_0^t dt' \Psi_D(z', t'; \tau) Q_D(z - z', t - t') + \Psi_D^0(z, t; \tau), \quad (17)$$

where $\psi_D(z, t)$ is the joint PDF of $Z(t)$ and the time elapsed t , i.e., $\psi_D(z, t) = \rho(t) \delta(z - t^\sigma)$, $\psi_D^0(z, t)$ is the joint PDF of $Z(t)$ and the first renewal at t , $\Psi_D(z, t; \tau)$ is the joint PDF of the displacement Z , the time elapsed t , and the last sojourn time given by τ , i.e., $\Psi_D(z, t; \tau) = \rho(\tau) \delta(z - \tau^{\sigma-1} t) \theta(\tau - t)$, and $\Psi_D^0(z, t; \tau)$ is the joint PDF of the displacement Z , the time elapsed t , and the last sojourn time τ . Finally, $P_D(z, t)$ can be obtained:

$$P_D(z, t) = \int_0^\infty d\tau P_D(z, t; \tau). \quad (18)$$

By the double Laplace transform, we have

$$\hat{P}_D(k, s) = \frac{\hat{\psi}_D^0(k, s) \int_0^\infty \hat{\Psi}_D(k, s; \tau) d\tau}{1 - \hat{\psi}_D(k, s)} + \int_0^\infty \hat{\Psi}_D^0(k, s; \tau) d\tau. \quad (19)$$

5. Equilibrium and Non-equilibrium Processes

5.1. Normal diffusion and fluctuation of the time-averaged MSD in equilibrium processes

In equilibrium processes, the PDFs related to the first recurrence times are given by $\psi_0(\mathbf{r}, t) = \int_0^\infty d\tau f_{\text{eq}}(\tau, t) \phi(\mathbf{r}, t; \tau)$ and $\Psi_0(\mathbf{r}, t; \tau) = \phi(\mathbf{r}, t; \tau) \int_t^\infty dt' f_{\text{eq}}(\tau, t')$.

Substituting these into Eq. (13), we obtain the Laplace transform of the MSD: $\langle \mathbf{r}(s)^2 \rangle_{\text{eq}} = \sum_{i=1}^n \frac{\partial^2 \hat{P}}{\partial \mathbf{k}_i^2} \Big|_{\mathbf{k}=\mathbf{0}} = \frac{2n}{s^2} \int_0^\infty d\tau \frac{\rho(\tau)}{\langle \tau \rangle} D_\tau \tau$. It follows that the MSD grows linearly with time in equilibrium processes:

$$\langle \mathbf{r}(t)^2 \rangle_{\text{eq}} = 2n \langle D(0) \rangle_{\text{eq}} t. \quad (20)$$

Moreover, the PDFs related to the first recurrence times in $Z(t)$ are given by $\psi_D^0(z, t) = \int_0^\infty d\tau f_{\text{eq}}(\tau, t) \delta(z - \tau^{\sigma-1} t)$ and $\Psi_D^0(z, t; \tau) = \int_t^\infty dt' f_{\text{eq}}(\tau, t') \delta(z - \tau^{\sigma-1} t) \theta(\tau - t)$. The Laplace transform of $\langle Z(t) \rangle$, denoted by $\langle \hat{Z}(s) \rangle$, is given by $\langle \hat{Z}(s) \rangle = - \frac{\partial \hat{P}_D(k, s)}{\partial k} \Big|_{k=0} = \int_0^\infty d\tau \frac{\rho(\tau) \tau^\sigma}{\langle \tau \rangle s^2}$. The inverse Laplace transform reads $Z(t) = \langle D(0) \rangle_{\text{eq}} t$. Hence, $\langle \delta^2(\Delta; t) \rangle_{\text{eq}} = 2n \langle D(0) \rangle_{\text{eq}} \Delta$. To characterize the irreproducibility of the time-averaged MSD, we calculate the relative standard deviation (RSD) studied in several diffusion processes [24, 47, 48]:

$$\Sigma(t; \Delta) \equiv \frac{\sqrt{\langle [\delta^2(\Delta; t) - \langle \delta^2(\Delta; t) \rangle]^2 \rangle}}{\langle \delta^2(\Delta; t) \rangle}. \quad (21)$$

We note that the RSD is independent of Δ because the time-averaged MSD depends linearly on Δ in the ATTM [see Eq. (14)]. If the time-averaged MSD is reproducible, then the RSD approaches zero as the measurement time t goes to infinity. It is important to note the RSD extracts a characteristic time from the system even when the time-averaged MSD is reproducible [49, 50, 37]. In particular, as will be shown below, a crossover time in the RSD is related to a characteristic time of fluctuating diffusivity if the instantaneous diffusivity changes over time. Obtaining the Laplace transform of $\langle Z^2(t) \rangle$ and inverting it, we have the asymptotic behavior of the squared RSD:

$$\Sigma^2(t; \Delta) \sim \frac{1}{t} \left(\frac{\langle \tau^2 \rangle}{\langle \tau \rangle} - \frac{2 \int_0^\infty d\tau \rho(\tau) \tau^{\sigma+1}}{\int_0^\infty d\tau \rho(\tau) \tau^\sigma} + \frac{\langle \tau \rangle \int_0^\infty d\tau \rho(\tau) \tau^{2\sigma}}{(\int_0^\infty d\tau \rho(\tau) \tau^\sigma)^2} \right) \quad (t \rightarrow \infty). \quad (22)$$

When $\rho(\tau)$ is the exponential distribution, the asymptotic behavior of the squared RSD decays as

$$\Sigma^2(t; \Delta) \sim \frac{\langle \tau \rangle}{t} \left(\frac{\Gamma(2\sigma + 1)}{\Gamma(\sigma + 1)^2} - 2\sigma \right) \quad (t \rightarrow \infty). \quad (23)$$

Thus, the RSD becomes zero when the measurement time goes to infinity. In other words, the time-averaged MSD is reproducible in the long-time measurements. On the other hand, for measurement times that are small compared with the characteristic time τ_c , the RSD does not decay:

$$\Sigma(t; \Delta) \cong \frac{\sqrt{\langle D(0)^2 \rangle_{\text{eq}} - \langle D(0) \rangle_{\text{eq}}^2}}{\sqrt{\langle D(0) \rangle_{\text{eq}}}} = \sqrt{\frac{\Gamma(2\sigma)}{\Gamma(1 + \sigma)^2} - 1} \quad (t \ll \tau_c). \quad (24)$$

Thus, there is a transition from constant RSD (irreproducible) to reproducible behavior, and the crossover time is related to a characteristic time like the mean sojourn time (see Fig. 2). The crossover time provides useful information on a characteristic time of fluctuating diffusivity, which has not been known so far.

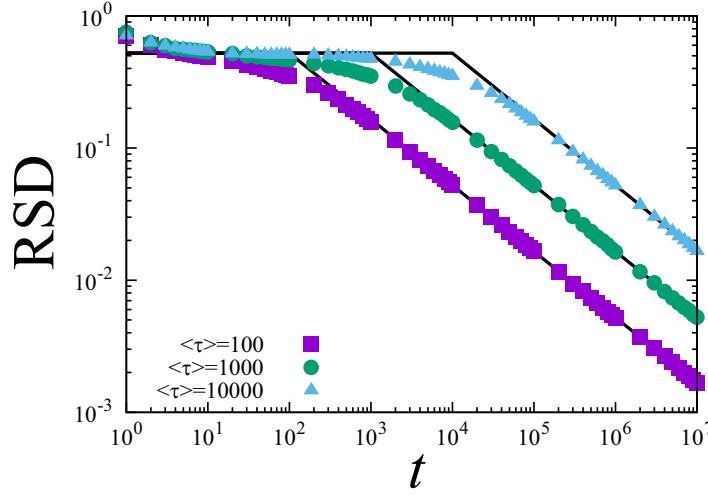


Figure 2. Relative standard deviation of the time-averaged MSD as a function of the measurement time ($\sigma = 0.8$). We used exponential distributions with different relaxation times for the sojourn time distribution. The lines represent the theory, i.e., Eqs. (23) and (24), while symbols show the results of numerical simulations.

5.2. Anomalous diffusion, aging, and distributional reproducibility in non-equilibrium processes

Here, we assume that the PDF of the sojourn time follows a power-law distribution $\rho(\tau)$ with exponent $\alpha < 1$. Because there is no equilibrium distribution for the forward recurrence time, this stochastic process is an intrinsic non-equilibrium process. If $\sigma > \alpha$, we note that the average of $2nD_t t$ with respect to the sojourn time t , i.e., the MSD during times when the state does not change, diverges because $\langle D_t t \rangle \equiv \int_0^\infty dt \rho(t) D_t t = \infty$. We consider a non-equilibrium situation in which the first renewal occurs at time $t = 0$. In this case, the generalized renewal equation is given by setting $\psi_0(\mathbf{r}, t) = 0$ and $\Psi_0(\mathbf{r}, t; \tau) = 0$ in Eqs. (8) and (9). Using the Laplace analysis as in the equilibrium case, we have the asymptotic behavior of $\langle \mathbf{r}(t)^2 \rangle$ for $t \rightarrow \infty$:

$$\langle \mathbf{r}(t)^2 \rangle \sim \begin{cases} \frac{2n\Gamma(\sigma-\alpha)}{|\Gamma(-\alpha)|(1+\alpha-\sigma)\Gamma(1+\sigma)} t^\sigma & (\sigma > \alpha), \\ \frac{2n}{|\Gamma(-\alpha)|\Gamma(1+\alpha)} t^\alpha \ln t & (\sigma = \alpha), \\ \frac{2n\langle D_t t \rangle}{c\Gamma(1+\alpha)} t^\alpha & (\sigma < \alpha). \end{cases} \quad (25)$$

Our theory provides the exact form of the MSD in the asymptotic limit, which matches perfectly with the results of numerical simulations without fitting the parameters (see Fig. 3). The exponent of subdiffusion is the same as that previously obtained (note that our notations are described by $\alpha = \sigma/\gamma$ and $\sigma = 1 - 1/\gamma$ in their notations) [30].

Next, we derive the ensemble average of the time-averaged MSD. The generalized renewal equation for $Z(t)$ is given by setting $\psi_D^0(z, t) = \delta(z)\delta(t)$ and $\Psi_D^0(z, t; \tau) = 0$ in

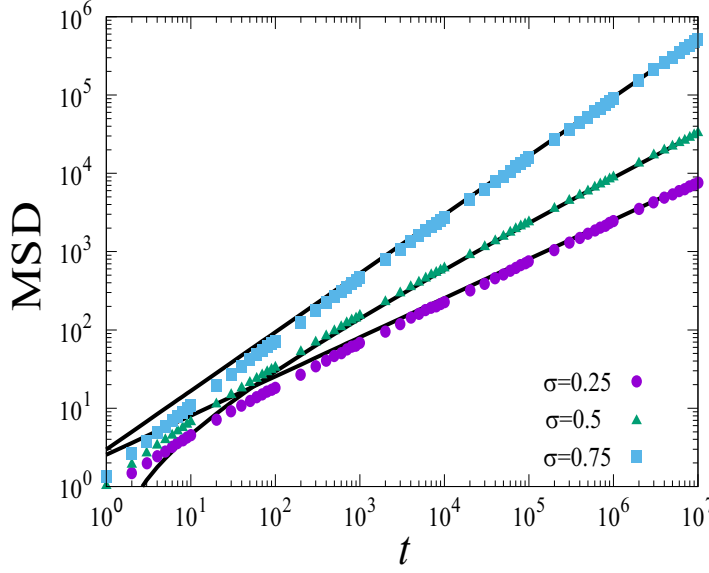


Figure 3. Mean square displacements for different σ ($\alpha = 0.5$ and $n = 1$). The lines represent the theory (25), while the symbols show the results of numerical simulations. Note that there are no fitting parameters.

Eqs. (16) and (17). Using the Laplace analysis on $P_D(z, t)$ as in the equilibrium case and using the relation $\langle \overline{\delta^2(\Delta; t)} \rangle \sim 2n\Delta \langle Z(t) \rangle / t$, we have

$$\langle \overline{\delta^2(\Delta; t)} \rangle \sim \begin{cases} \frac{2n\Delta\Gamma(\sigma-\alpha)}{|\Gamma(-\alpha)|(1+\alpha-\sigma)\Gamma(1+\sigma)} t^{\sigma-1} & (\sigma > \alpha), \\ \frac{2n\Delta}{|\Gamma(-\alpha)|\Gamma(1+\alpha)} t^{\alpha-1} \ln t \left(1 + \frac{1}{\ln t}\right) & (\sigma = \alpha), \\ \frac{2n\Delta\langle D_t t \rangle}{c\Gamma(1+\alpha)} t^{\alpha-1} & (\sigma < \alpha). \end{cases} \quad (26)$$

Therefore, the ensemble average of the time-averaged MSD shows aging: $\langle \overline{\delta^2(\Delta; t)} \rangle \rightarrow 0$ ($t \rightarrow \infty$). Figure 4 shows that this aging behavior is clearly described by Eq. (26). This exact form in the asymptotic limit has also been obtained for the first time.

Moreover, we obtain the second moment of $Z(t)$ (see Appendix. A):

$$\langle \hat{Z}(t)^2 \rangle \sim \begin{cases} \left(\frac{2\Gamma(2\sigma-\alpha)}{|\Gamma(-\alpha)|(2+\alpha-2\sigma)} + \frac{2\Gamma(\sigma-\alpha)^2}{|\Gamma(-\alpha)|^2(1+\alpha-\sigma)} \right) \frac{t^{2\sigma}}{\Gamma(1+2\sigma)} & (\sigma > \alpha), \\ \frac{2}{|\Gamma(-\alpha)|^2} \frac{(t^\alpha \ln t)^2}{\Gamma(2\alpha+1)} & (\sigma = \alpha), \\ \frac{2\langle D_t t \rangle^2}{c^2} \frac{t^{2\alpha}}{\Gamma(2\alpha+1)} & (\sigma \leq \alpha). \end{cases} \quad (27)$$

It follows that the RSD is given by

$$\Sigma^2(t; \Delta) \sim \begin{cases} \frac{2(1+\alpha-\sigma)\Gamma(1+\sigma)^2}{\Gamma(1+2\sigma)} \left(\frac{(1+\alpha-\sigma)\Gamma(2\sigma-\alpha)|\Gamma(-\alpha)|}{(2+\alpha-2\sigma)\Gamma(\sigma-\alpha)^2} + 1 \right) - 1 & (\sigma > \alpha), \\ \frac{2\Gamma(1+\alpha)^2}{\Gamma(2\alpha+1)} - 1 & (\sigma \leq \alpha), \end{cases} \quad (28)$$

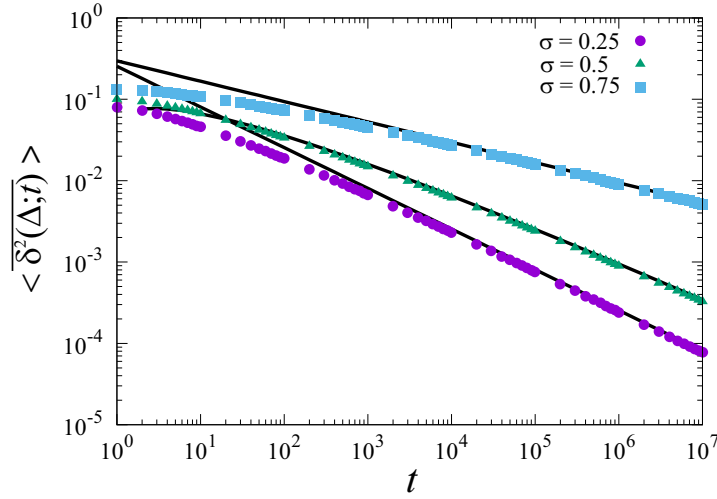


Figure 4. Ensemble average of the time-averaged MSD as a function of the measurement time t for different σ ($\alpha = 0.5$ and $n = 1$). The lines represent the theory (26), while the symbols show the results of numerical simulations. Note that there are no fitting parameters.

in the asymptotic limit of $t \rightarrow \infty$. Therefore, the RSD does not decay even in the long-time limit for the measurement time. The theory of the RSD has been confirmed in numerical simulations (see Fig. 5). This is direct evidence of irreproducibility. We note that the value of the RSD for $\sigma \leq \alpha$ is the same as that in a continuous-time random walk [24].

Furthermore, we can show that all of the higher moments are given by

$$\langle \hat{Z}(t)^k \rangle \sim \begin{cases} \frac{M_k(\alpha, \sigma)}{|\Gamma(-\alpha)|} \frac{t^{k(1-\sigma)}}{\Gamma(k+1-k\sigma)} & (\sigma > \alpha) \\ \frac{k! \langle D_t t \rangle^k}{c^k} \frac{t^{k\alpha}}{\Gamma(k\alpha+1)} & (\sigma \leq \alpha), \end{cases} \quad (29)$$

where the coefficient $M_k(\alpha, \sigma)$ is given in Appendix A. Because $Z(t)/t$ is the time-averaged diffusion coefficient, the distribution of the normalized time-averaged diffusion coefficient, $\overline{D}_t \equiv \overline{\delta^2(\Delta; t)} / \langle \delta^2(\Delta; t) \rangle \sim Z(t) / \langle Z(t) \rangle$, does not converge to a delta function like ergodic observables but converge to a broad distribution. Moreover, the distribution of time-averaged diffusion coefficients obtained from single trajectories is universal in the sense that it does not depend on the initial conditions nor noise histories. Therefore, time-averaged diffusion coefficient has a distributional reproducibility in the ATTM when the exponent is less than one.

6. Discussion

We have described rigorous equations for the propagator, Eqs. (8) and (9), and the time-averaged MSD, Eqs. (16) and (17), in ATTM. By solving these equations, we have obtained exact solutions for the MSD and the moments of the time-averaged MSD.

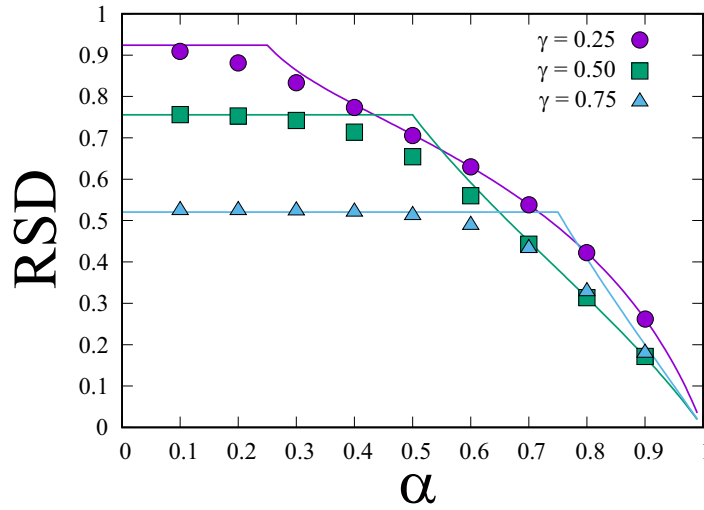


Figure 5. Relative standard deviation of the time-averaged MSD as a function of α ($\sigma = 0.25, 0.5$, and 0.75). In numerical simulations, we use $\Delta = 0.1$ for calculating the RSD. The dashed lines represent the theory described by Eq. (28), while the symbols show the results of numerical simulations.

In equilibrium processes, we found a transition from irreproducible to reproducible behavior in the time-averaged MSD and extracted the characteristic time using the crossover time. However, the RSD does not decay at all in non-equilibrium processes. We have provided theoretical evidence for distributional reproducibility of the time-averaged MSD in heterogeneous environments. Distributional behaviors for the time-averaged MSD obtained here are closely related to the distributional limit theorem of a non-integrable observation function in infinite ergodic theory [51]. This is because the moments obtained here are similar to those in [51]. In other words, the distribution looks the same in shape.

A quenched model, called the quenched radius model (QRM), was also considered in [30]. By analogy to the relationship between the quenched trap model and the annealed model (continuous-time random walk) [52, 53, 27, 29], we conjecture that the exponent of the MSD as well as the moments of the time-averaged MSD in QRM will be the same as those in ATTM when the dimension is greater than two. However, it should be noted that the MSD and the moments of the time-averaged MSD differ when the dimension is less than two. In fact, the subdiffusive exponent in the QRM is given by $2\alpha/(1 + \alpha)$ in the one-dimensional case when the second moment of patch size does not diverge [30]. Thus, the ergodic properties for one-dimensional QRM will be different from those for ATTM, which is still an interesting open problem.

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References

- [1] Golding I and Cox E C 2006 *Phys. Rev. Lett.* **96** 098102
- [2] Jeon J H, Tejedor V, Burov S, Barkai E, Selhuber-Unkel C, Berg-Sørensen K, Oddershede L and Metzler R 2011 *Phys. Rev. Lett.* **106**(4) 048103
- [3] Weigel A, Simon B, Tamkun M and Krapf D 2011 *Proc. Natl. Acad. Sci. USA* **108** 6438
- [4] Tabei S A, Burov S, Kim H Y, Kuznetsov A, Huynh T, Jureller J, Philipson L H, Dinner A R and Scherer N F 2013 *Proc. Natl. Acad. Sci. USA* **110** 4911–4916
- [5] Höfling F and Franosch T 2013 *Rep. Prog. Phys.* **76** 046602
- [6] Manzo C, Torreno-Pina J A, Massignan P, Lapeyre Jr G J, Lewenstein M and Parajo M F G 2015 *Phys. Rev. X* **5** 011021
- [7] Barkai E, Garini Y and Metzler R 2012 *Phys. Today* **65** 29
- [8] Granéli A, Yeykal C C, Robertson R B and Greene E C 2006 *Proc. Natl. Acad. Sci. USA* **103** 1221
- [9] Wang Y M, Austin R H and Cox E C 2006 *Phys. Rev. Lett.* **97**(4) 048302
- [10] Brokmann X and *et al* 2003 *Phys. Rev. Lett.* **90** 120601
- [11] Stefani F D, Hoogenboom J P and Barkai E 2009 *Phys. Today* **62** 34–39
- [12] Takeuchi K A and Akimoto T 2015 *arXiv:1509.03082*
- [13] Darling D A and Kac M 1957 *Trans. Am. Math. Soc.* **84** 444–458
- [14] Lamperti J 1958 *Trans. Am. Math. Soc.* **88** 380–387
- [15] Dynkin E 1961 *Selected Translations in Mathematical Statistics and Probability (American Mathematical Society, Providence)* **1** 171
- [16] Birkhoff G D 1931 *Proc. Natl. Acad. Sci. USA* **17** 656–660
- [17] Aaronson J 1997 *An Introduction to Infinite Ergodic Theory* (Providence: American Mathematical Society)
- [18] Thaler M and Zweimüller R 2006 *Probab. Theory Relat. Fields* **135** 15–52
- [19] Akimoto T and Miyaguchi T 2010 *Phys. Rev. E* **82** 030102(R)
- [20] Akimoto T 2012 *Phys. Rev. Lett.* **108**(16) 164101
- [21] Lutz E and Renzoni F 2013 *Nat. Phys.* **9** 615–619
- [22] Bouchaud J P 1992 *J. Phys. I* **2** 1705–1713
- [23] Lubelski A, Sokolov I M and Klafter J 2008 *Phys. Rev. Lett.* **100** 250602
- [24] He Y, Burov S, Metzler R and Barkai E 2008 *Phys. Rev. Lett.* **101** 058101
- [25] Metzler R, Jeon J H, Cherstvy A G and Barkai E 2014 *Phys. Chem. Chem. Phys.* **16** 24128–24164
- [26] Feller W 1968 *An Introduction to Probability Theory and Its Applications* vol 1 (Wiley, New York)
- [27] Miyaguchi T and Akimoto T 2011 *Phys. Rev. E* **83** 031926
- [28] Akimoto T and Miyaguchi T 2013 *Phys. Rev. E* **87**(6) 062134
- [29] Miyaguchi T and Akimoto T 2015 *Phys. Rev. E* **91**(1) 010102
- [30] Massignan P, Manzo C, Torreno-Pina J A, García-Parajo M F, Lewenstein M and G J Lapeyre J 2014 *Phys. Rev. Lett.* **112** 150603
- [31] Uneyama T, Miyaguchi T and Akimoto T 2015 *Phys. Rev. E* **92**(3) 032140
- [32] Akimoto T and Yamamoto E 2016 *Phys. Rev. E* **93**(6) 062109
- [33] Rozenfeld R, Luczka J and Talkner P 1998 *Physics Letters A* **249** 409–414
- [34] Luczka J, Talkner P and Hänggi P 2000 *Physica A* **278** 18–31
- [35] Beck C and Cohen E 2003 *Physica A* **322** 267–275
- [36] Luczka J, Niemiec M and Hänggi P 1995 *Phys. Rev. E* **52**(6) 5810–5816
- [37] Akimoto T and Seki K 2015 *Phys. Rev. E* **92**(2) 022114
- [38] Miyaguchi T, Akimoto T and Yamamoto E 2016 *Phys. Rev. E* **94**(1) 012109
- [39] Helfferich J, Ziebert F, Frey S, Meyer H, Farago J, Blumen A and Baschnagel J 2014 *Phys. Rev. E* **89**(4) 042603
- [40] Cox D R 1962 *Renewal theory* (London: Methuen)
- [41] Godrèche C and Luck J M 2001 *J. Stat. Phys.* **104** 489–524
- [42] Montroll E W and Weiss G H 1965 *J. Math. Phys.* **6** 167–181

- [43] Scher H and Lax M 1973 *Phys. Rev. B* **7**(10) 4491–4502
- [44] Shlesinger M, Klafter J and Wong Y 1982 *J. Stat. Phys.* **27** 499–512
- [45] Shlesinger M F, West B J and Klafter J 1987 *Phys. Rev. Lett.* **58**(11) 1100–1103
- [46] Akimoto T and Miyaguchi T 2014 *J. Stat. Phys.* **157** 515
- [47] Deng W and Barkai E 2009 *Phys. Rev. E* **79** 011112
- [48] Akimoto T, Yamamoto E, Yasuoka K, Hirano Y and Yasui M 2011 *Phys. Rev. Lett.* **107**(17) 178103
- [49] Miyaguchi T and Akimoto T 2011 *Phys. Rev. E* **83** 062101
- [50] Uneyama T, Akimoto T and Miyaguchi T 2012 *J. Chem. Phys.* **137** 114903–114903
- [51] Akimoto T, Shinkai S and Aizawa Y 2015 *J. Stat. Phys.* **158** 476–493
- [52] Machta J 1985 *J. Phys. A* **18** L531
- [53] Bouchaud J and Georges A 1990 *Phys. Rep.* **195** 127–293

Appendix A. n th moment of $Z(t)$

The n th derivative of $\hat{P}(k, s)$ satisfies the following recursion relation:

$$\begin{aligned} \hat{P}_D^{(n)}(k, s) = & \frac{1}{1 - \hat{\psi}_D(k, s)} \left[\sum_{i=1}^{n-1} c_{n,i} \hat{P}_D^{(i)}(k, s) \hat{\psi}_D^{(n-i)}(k, s) + \hat{P}_D(k, s) \hat{\psi}_D^{(n)}(k, s) \right. \\ & \left. + \int_0^\infty d\tau \rho(\tau) \hat{\Psi}_D^{(n)}(k, s; \tau) \right], \end{aligned} \quad (\text{A.1})$$

where $c_{n,i} = c_{n-1,i} + c_{n-1,i-1}$ ($i = 2, \dots, n-2$) and $c_{n,n-1} = c_{n,1} = n$. Here, we assume that

$$\hat{P}_D^{(i)}(0, s) \sim (-1)^n \frac{M_i(\alpha, \sigma)}{|\Gamma(-\alpha)|} \frac{1}{s^{1+i\sigma}}. \quad (\text{A.2})$$

It follows that

$$\hat{P}^{(n)}(0, s) = \left[\sum_{i=1}^{n-1} c_{n,i} (-1)^n M_i(\alpha, \sigma) \frac{\Gamma((n-i)\sigma - \alpha)}{|\Gamma(-\alpha)|} + \frac{n}{n + \alpha - n\sigma} \Gamma(n\sigma - \alpha) \right] \frac{1}{|\Gamma(-\alpha)| s^{1+n\sigma}}. \quad (\text{A.3})$$

Therefore,

$$M_n(\alpha, \sigma) = (-1)^n \sum_{i=1}^{n-1} c_{n,i} M_i(\alpha, \sigma) \frac{\Gamma((n-i)\sigma - \alpha)}{|\Gamma(-\alpha)|} + \frac{n}{n + \alpha - n\sigma} \Gamma(n\sigma - \alpha). \quad (\text{A.4})$$